Loose ends

The seven deadly curs'd sins ... Pride

Dear Willie,

I received your package last Monday and have spent the week reading its contents. You have no idea of how grateful I am to have something to do these days. The experiments validating your new theory of olfaction are most ingenious. Then I read the letter from the editor of *Smell* and the referees' comments enclosed. You can safely ignore the editor who has clearly not read the paper. The first referee can also be set aside as all of his comments came straight out of a word processor. However, the second referee, who seems to have angered you most, should be taken more seriously.

I know that you are proud of your work but, like most things, pride has two faces: true and false, honest and misapplied. When it is based on real quality and attainment it is a virtue, but when the self esteem is overdone it is a vice. It is not impossible that a referee has seen something you have not seen, knows something unknown to you or, by sheer chance, has found some gap in your argument. You should therefore go and do the added control, if only to prove him wrong.

I remember reviewing a paper in which the authors proudly claimed to have rescued galactokinase-negative mutant human cells with DNA from a lambda bacteriophage carrying the galactose operon of *E. coli*. The control was a normal lambda. I just did not believe the result and I suggested doing the same experiment with a nonsense mutation in the galactokinase gene. This is a text book control experiment because the two phages would differ only in one base pair. The authors' reply was that they saw no point in doing this control because it was bound not to work. Today, of course, we know that the original result is totally implausible. The authors were either misled by an artefact — perhaps carried over enzyme from the lysed bacteria — or this was a case of applying the UNF (universal normalizing factor), which is to multiply the experimental result by the ratio of the theoretical to the experimental result.

The episode I want to recount now is much more instructive. In 1960, I attended a seminar by a scientist, G (because some of the people are still alive I shall not disclose their names), who announced with great pride the result of an experiment which he believed showed that bacteriophages with every thymine in their DNA substituted by bromouracil produce no mutants at all. Since G took great delight in the demolition of standard theories of molecular biology, such as the complementary base pair mechanism of DNA replication, he was immensely pleased to show that the doctrine that base analogue incorporation in DNA causes mutation was absolutely wrong. After a few desultory questions from the audience, I got up and said "I bet you this is wrong". "How can it be wrong?", he retorted, "we have done all the controls". "Never mind", I said, "do you take the bet?". "Of course", came the reply. "The bet will be one bottle of champagne — and French, not Californian", I said, and, turning to the audience, asked "who else takes the bet?". A colleague, F, immediately sided with me, while M joined G; all the others sat gaping.

I then outlined the control experiment, which was to repeat the entire experiment, but to leave out the bromodeoxyuridine. I predicted that the same result would be obtained, even though that sounded ridiculous, and promised to explain why, if I was right, which I was. For you to understand what was going on, I have to give some details of the experiment. It involved measuring the reversion of *r*II mutants of bacteriophage T4 to r^+. The wild type grows with lysis inhibition both on the standard B strain of *E. coli*, and also on *E. coli* K12, on which *r*II mutants make no plaques at all. The *r*II phages were labelled by infecting a culture of strain B in the presence of 5-bromodeoxyuridine and growing to lysis. This phage was then mixed with some r^+ and the mixture was centrifuged to equilibrium in a CsCl density gradient. The *r*II phages banded at a greater density than the r^+ phages and indeed the difference was consistent with the complete substitution by bromouracil of the thymine in the phage DNA.

Now, I knew two things that G didn't. The first is that *E. coli* has an inducible enzyme that cleaves the bromodeoxyuridine to bromouracil, which is not assimilated. I therefore knew that the phages could not have contained any bromouracil. Secondly, a few years earlier, Sewell Champe and I had attempted to measure the size of *r*II deletions by density gradient centrifugation and to our astonishment found that they were heavier than r^+. We rapidly traced this to the fact that growth under conditions of lysis inhibition made phages lighter, regardless of genotype. By coincidence, the density difference corresponded to complete substitution of thymine by bromouracil.

I can't say I was proud of winning my bet because it was too easy and, anyway, I had private information so it was a bit unfair. But I took great pleasure in puncturing false pride. G paid the debt, but in Californian champagne. M never paid, but his sin was merely to have been seduced by what seemed to be a certainty, and perhaps he felt that enduring my many reminders of this painful debt was payment enough. As ever,

Uncle Syd